Remarks/Arguments

Claims 25 and 26 are withdrawn. Claim 13 has been amended for a typographical error. Subsequent to the entry of the present amendment, claims 1-25 and 27-29 are pending and at issue. Reconsideration of the application is respectfully requested in view of the following remarks.

Rejections under 35 U.S.C. § 103

Claims 1-24 and 27-29 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Merrified et al. (PCT Publication No. WO 00/37169) in view of Manning et al. (U.S. Patent No. 5,770,559). Applicants respectively traverse this rejection.

The Office Action alleges that the "Merrified et al. publication discloses a process and apparatus for the production of particles using a solvent/anti-solvent process in which the anti-solvent is preferably a supercritical fluid (see Abstract). Suitable anti-solvents include ethane and ethylene. The anti-solvent stream may further comprise a modifier, such as methanol and ethanol (see Page 5, Line 19 to Page 6, Line 4). The compressible anti-solvent may be introduced at pressures of 50 to 100 bar at suitable temperature, which is likely to be in the range of 1.01 T_C to 4.0 T_C (See Page 6, Lines 5-12; and Page 12, Lines 19-25). The apparatus may include a means for collection of the particles, such as a collection chamber (See Page 16, Lines 21-29). The particles may be a pharmaceutical material, with a small particle size, such as around 1 to 20 microns (See Page 18, Lines 7-9)." The Office Action further alleges that Merrified does not explicitly disclose insulin as a pharmaceutical material, but that Manning does disclose a solvent/anti-solvent process for precipitation of particles and that insulin is mentioned as a pharmaceutical substance. The Office Action finally alleges that it would have been obvious to one of ordinary skill in the art to combine the disclosures of the prior art in order to obtain the instantly claimed invention.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify a reference or to combine the teachings of multiple references. Second, there must be a reasonable expectation of success. Third, the prior art must teach or suggest all of the recited claim limitations. Of course, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure.

Firstly, we submit that it is not at all obvious that one of ordinary skill in the art would be motivated to combine the disclosures of Merrified et al. and Manning et al. We submit that it would be extremely unlikely that one of ordinary skill in the art would be motivated to combine two disclosures that describe processes that are quite different, in that one involves a supercritical antisolvent whereas the other is looking to create hydrophobic ion pairs to solubilize an active in a solvent in which it is not ordinarily soluble, followed by precipitating particles of the active (as discussed further below). One of ordinary skill in the art would be aware that the exact steps in a supercritical process are quite specific to the type of supercritical process being employed and that using substantially different parameters and/or reagents could well have an impact on the outcome of the process.

Merrified et al. describes a process and apparatus for the production of particles of a material in which a stream of a dispersion of the material in the solvent and a stream of compressible fluid anti-solvent substance are mixed under conditions such that the substance is in a compressible fluid anti-solvent state. The anti-solvent is preferably a supercritical fluid. Whilst the solution and anti-solvent are mixed at pressure, the ratios of the components along with the conditions at the point of mixing are such that the precipitation of the material (i.e. the solute) does not occur at the point of mixing. Indeed, after the two streams are mixed, the mixture then flows along a conduit towards an orifice from which it flows into a downstream region in which the compressible fluid anti-solvent substance decompresses and the solute

precipitation occurs downstream from the point of contact of the two fluid streams. (see, for example, Merrified, page 3, line 27 to page 4, line 7).

Merrified et al. process differs from the method claimed in the present patent application. The claimed method involves contacting a non-gaseous fluid containing the substance of interest with a dense gas which includes an anti-solvent and a modifying agent. In the claimed method, when the stream of non-gaseous fluid and the stream of dense gas come into contact, resulting in expansion of non-gaseous fluid and precipitation of the substance of interest occurs immediately. Therefore, in the claimed method, the substance precipitates at the point of contact of the fluid streams, not at a point downstream of the point of contact, as occurs in Merrified et al.

In this way, the process of Merrified et al. is akin to a RESS (Rapid Expansion of Supercritical Solutions) process, where particles are dissolved in a dense fluid which is then rapidly expanded into a low temperature and pressure environment. This sudden change in conditions causes rapid crystallization of the solute as micronised particles. In contrast, the method of the present invention is more akin to an ASES (Aerosol Solvent Extraction System) process, where a bulk drug solution is sprayed into a dense fluid environment. The droplets of the drug solvent expand rapidly, resulting in a rapid precipitation as the drug passes from a solvent environment to an antisolvent environment in a very short period of time. The claim requires the contacting of the dense gas "to expand the fluid".

As can be seen from the above description of RESS and ASES, the process of Merrified et al. is more akin to a RESS process substance as the stream of solution of a material and the stream of the compressed antisolvent are mixed, travel downstream and are passed into an area of low pressure and low temperature where the compressed antisolvent substance depressurizes causing precipitation.

In contrast, the method of the present invention results in precipitation of the substance at the point of contact between the stream of solution of the substance and the stream of antisolvent, the precipitation occurring in an area that is still pressurized.

Since many biologically active substances are very sensitive to changes in pH and also the solvent environment, it is desirable to minimize the contact of such substances with changes of pH or organic solvents which may lead to changes in the biological activity and/or structure of the substance.

As can be seen from paragraph [0020] of the present application maintaining structure and/or activity, particularly biological activity was a specific consideration of the present invention. Specifically the choice of antisolvent is an important consideration (see paragraph [0013]). Merrified et al. broadly states that the process is suitable for use with materials which are pharmaceutical materials. There is no contemplation in Merrified et al. that not all pharmaceutical materials would be suited for use in that process, since many may be irreversibly changed (e.g., in terms of structure and/or biological activity etc) as a result of the process. Indeed, page 5, lines 22-24 of Merrified et al., where suitable antisolvents are discussed, it states ". . . carbon dioxide is preferred, inter alia because it is cheap, non-flammable, non-toxic and environmentally benign . . .". Thus the choice of antisolvent is based on practical issues, rather than concerns for the integrity of the pharmaceutical material being processed. However, carbon dioxide does have an effect on the pH of an aqueous solution due to carbonic acid formation.

Manning et al. relates to a method for preparing a true, homogeneous solution of a pharmaceutical substance dissolved in an organic solvent in which the pharmaceutical substance is not normally soluble. The solution may then be further processed to prepare pharmaceutical powders. The true solution is prepared by forming a hydrophobic ion pair complex involving the pharmaceutical substance and an amphiphilic material. This is a completely different process

from that of the present invention. The method of the present invention does not involve the use of hydrophobic ion pair complexes. While it is true that insulin is listed as a pharmaceutical substance suitable for use in the Manning et al. process (column 5, line 41 to column 6, line 9), it is merely one of a large number of potentially suitable pharmaceutical substances listed.

We therefore submit that claim 1 of the present application is not obvious in light of Merrified et al. and Manning et al. for the reasons stated above. In addition, given the discussion above in relation to the selection of antisolvent in Merrified et al., we further submit that claim 2 is not obvious in light of Merrified et al. and Manning et al. because there is no contemplation in the prior art that the antisolvent may alter the pH of the non-gaseous fluid which would lead to changes in the structure and/or biological activity of the material of interest. Accordingly, for at least the reasons given above, Applicants respectfully request that the rejection of independent claim 1, and dependent claims 2-24 and 27-29 under 35 U.S.C. §103 be withdrawn.

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

A check in the amount of $60.00 is enclosed to cover the One Month Extension of Time fee. No additional fee is believed due in connection with this Response. However, The Commissioner is hereby authorized to charge any fees that may be associated with this communication, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

Date: September 6, 2005

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